Am J Cancer Res 2024;14(7):3523-3532
www.ajcr.us /ISSN:2156-6976/ajcr0154728

Original Article

Efficacy of first-line combination therapies versus gemcitabine monotherapy for advanced pancreatic cancer: a systematic review and network meta-analysis

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Received December 2, 2023; Accepted June 12, 2024; Epub July 15, 2024; Published July 30, 2024

Abstract: Various first-line gemcitabine-based or fluorouracil-based combination regimens were approved in patients with advanced pancreatic cancer. Recent randomized clinical trials (RCTs) have investigated chemotherapy backbones in combination with novel investigational drugs, including chemotherapy agents or targeted drugs. However, the comparative efficacy of these different combination therapies remains limited. This systematic review and network meta-analysis aimed to assess the efficacy of first-line combination therapies for advanced pancreatic cancer. The study included 46 RCTs with 10,499 patients and 47 distinct regimens, using data sources from MEDLINE, EMBASE, Cochrane Clinical Trials, and ClinicalTrials.gov from January 1, 2010 to April 23, 2024. The primary outcomes were overall survival (OS) and progression-free survival (PFS), while secondary outcomes included overall response rate (ORR) and disease control rate (DCR). The analysis revealed that gemcitabine+nab-paclitaxel (GA), GA with platinum and fluorouracil (GA+Plat+FU), gemcitabine with fluorouracil (G+FU), G+Plt+FU, and FOLFIRINOX were associated with superior OS and PFS compared to gemcitabine monotherapy. Triplet or quadruplet polychemotherapy combinations, such as GA+Plat+FU, G+Plt+FU, and FOLFIRINOX, demonstrated better OS benefit with hazard ratios of 0.42 (95% CI, 0.26-0.68), 0.41 (95% CI, 0.24-0.71), and 0.58 (95% CI, 0.48-0.71), respectively, compared to doublet regimens like GA and G+FU, which had hazard ratios of 0.70 (95% CI, 0.59-0.82) and 0.82 (95% CI, 0.72-0.95), respectively. Notably, no targeted drugs, monoclonal antibodies, or other medications showed improved survival when added to chemotherapy backbones. These findings support the use of gemcitabine-based or fluorouracil-based triplet or quadruplet regimens for better survival outcomes in patients with advanced pancreatic cancer. Further research is warranted to explore the potential benefits of adding chemotherapy agents, such as fluorouracil, to the GA doublet regimen.

Keywords: Advanced pancreatic cancer, first-line combination therapy, network meta-analysis, gemcitabine-based treatment, fluorouracil-based treatment

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the leading cause of cancer death worldwide, with a 5-year survival rate of 10% [1]. Approximately 80% of patients with PDAC were unresectable with locally advanced or metastatic disease [2]. The standard upfront treatment for advanced PDAC is chemotherapy. As single-agent gemcitabine demonstrated superior clinical benefit from a randomized trial in 1997, gemcitabine has become the mainstay of chemotherapy regimens for advanced PDAC [3]. However, the efficacy of gemcitabine monotherapy remained poor with median survival of 4-6 months [4].

Combination chemotherapy regimens have been developed to improve the survival in advanced pancreatic cancer. 5-fluorouracil, nab-paclitaxel, platinum, and irinotecan are active agents exerting anti-tumor effect on PDAC cells. Several combination treatments have become new standard regimens: nab-

https://doi.org/10.62347/TQRB4608

paclitaxel with gemcitabine (GA), 5-FU with irinotecan and oxaliplatin (FOLFIRINOX), irinotecan with 5-FU/leucovorin, and gemcitabine with S-1 [5-8]. Moreover, several randomized phase II trials have explored the efficacy of gemcitabine in combination with various targeted drugs, such as erlotinib, an epidermal growth factor receptor inhibitor, which has shown improved survival outcomes [9].

The evolution of combination chemotherapy in pancreatic cancer continues, with great enthusiasm focusing on the incorporation of new chemotherapy, targeted drugs or monoclonal antibodies along with chemotherapy backbone into doublet, triplet, and even quadruplet regimens. While previous work explored efficacy among different chemotherapy regimens [10-12], the thorough investigation of first-line combined treatments involving chemotherapy, small-molecule targeted drugs, monoclonal antibodies, or other medications remains limited.

Given the variability of treatment combinations, there is a compelling need for conducting a network meta-analysis (NMA) to address the optimal first-line systemic treatment. This statistical approach can integrate data from diverse studies and indirectly compare the efficacy across different treatment regimens. This will provide valuable insights for clinical decision-making and facilitate the development of future clinical trials for patients with advanced PDAC.

Methods

Literature search and study selection

This systemic review-NMA (SR-NMA) was conducted and reported following the PRISMA-NMA extension statement [13], and was registered on PROSPERO (CRD42023406207). Two authors (Y-L H and S-Y W) conducted a comprehensive search for randomized controlled trials in Embase, MEDLINE, Cochrane Library, and ClinicalTrials.gov. Our study specifically focused on advanced pancreatic adenocarcinoma, including unresectable cancer and locally advanced cancer, and examined first-line combined treatments consisting of chemotherapy, monoclonal antibodies, and targeted drugs. The search terms were tailored to different databases such as “advanced pancreatic neoplasms” and “drug therapy”. Supplementary Table 1 provides detailed information on the search strategies employed along with appropriate filters. We included only phase II or III randomized controlled trials (RCTs) with at least two comparable arms that were published as original articles or registered trials since 2010, as modern polychemotherapy regimens including GA and FOLFIRINOX were published in 2013 and 2011, respectively [5, 6]. We limited our search to articles published in English. No restrictions were placed on age, gender, or race during the search process. The last date of the literature search was April 23th, 2024. Duplicate articles were automatically removed using Mendeley (Version 1.19.8). Initial screening and review of articles were conducted by Y-L H, W-K H, and S-Y W, with any discrepancies resolved through consensus or consultation with another independent author (C-N Y). We excluded trials that did not employ the intention-to-treat (ITT) method and trials involving non-commercialized medications. The final selection of articles for statistical synthesis was approved by another independent author (C-N Y).

Outcome measures

The primary outcomes were overall survival (OS) and disease-free survival (DFS), and the secondary outcomes were objective response rate (ORR) and disease control rate (DCR).

Categorization of combined treatment

The first-line systemic treatments for advanced pancreatic cancer comprised a chemotherapy backbone combined with a variety of investigational drugs, including either additional chemotherapy, small-molecule targeted drugs, tyrosine kinase inhibitors, monoclonal antibodies, or other medications. We summarize the categorization of different drug classes in **Table 1**.

Data extraction and quality assessment

The data on tumor location, Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance status (KPS), extent of disease, and efficacy outcomes were retrieved from enrolled articles. For categorical data, we recorded the number of events and the total number of cases. For time-to-event data, we obtained the hazard ratio (HR) with a 95% confidence interval (CI) and the median with a 95% CI. In cases

Table 1. The categorization of combined drug therapies

FOLFIRINOX	Folinic acid, fluorouracil, irinotecan, oxaliplatin
GA	Gemcitabine and nab-paclitaxel
G	Gemcitabine
A	Nab-paclitaxel
Plat	Cisplatin or oxaliplatin
mAB[a]	Bevacizumab, Cetuximab, Ganitumab, Conatumumab, Aflibercept, Simtuzumab, Panitumumab, Ramucirumab, and Tarextumab
Targeted[b]	Enzastaurin, Upamostat, Rigosertib, and Apatorsen
TKI[c]	Sorafenib, Trametinib, Sunitinib, Erlotinib, Dasatinib, Vandetanib, and Ibrutinib
FU[d]	S-1 and Capecitabine
FOLFIRI	Folinic acid, fluorouracil, and irinotecan
HCQ	Hydroxychloroquine
Other	Kanglaite, Imexon, Necuparanib, Simvastatin, and Metformin

[a]monoclonal antibodies; [b]small-molecule targeted drugs; [c]tyrosine kinase inhibitor; [d]oral 5-fluorouracil.

where articles did not provide HR and 95% CI data, we followed a standardized approach and reconstructed the data using Kaplan-Meier curves [14]. The process of data extractions was conducted by three authors (Y-L H, W-K H, and S-Y W).

The quality assessment of the included studies was performed independently by four authors (Y-L H, W-K H, C-N W, and S-Y W) using RevMan 5.4. The assessment utilized a risk of bias tool that encompassed six domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended intervention, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, (5) bias in the selection of the reported result, and (6) overall bias [15]. Each domain was evaluated and categorized as either low risk, some concerns, or high risk. Any disagreement among authors was solved by a consensus or seeking consultation from another author (C-N Y).

Statistical analysis

The NMA is conducted with a frequentist approach. The NMA is conducted based on the categorization (**Table 1**). Nevertheless, the study arms in our enrolled trials are complex as each study arm may contain multiple drugs. In the traditional NMA, interventions are typically compared as a whole, considering their overall effects; therefore, simply conducting the traditional NMA can not estimate the individual effect of each component. To address this, we furtherly applied the component NMA (cNMA) model. This approach involves breaking down the intervention into its individual components (different medications) and analyzing their effects separately, as well as examining the combined effect when these components are administered together.

We also conducted a comprehensive assessment of the original treatment arm without any categorization. To evaluate the heterogeneity, we utilize the I^2 statistics, where values between 0% and 25% indicate low heterogeneity, 25% to 50% indicate medium heterogeneity, and values greater than 50% indicate substantial heterogeneity. If substantial heterogeneity was observed, further subgroup analysis would be conducted. Since the concept of NMA is not to seek an identical effect from interventions, but to identify optimal interventions from different trials, the random-effects model (REM) was applied for this study. For the evaluation of incoherence, the Separating Indirect from Direct Evidence (SIDE) approach was used to examine whether there is a discrepancy between direct and indirect evidence. Given the inclusion of multi-arm trials, inconsistency was also assessed using the design-by-treatment random effect model [16, 17]. Funnel plot and Egger's test were used to assess potential publication bias. To rank all the interventions, the surface under the cumulative ranking (SUCRA) are calculated for both NMA and cNMA results. The *p*-value lesser than 0.05 is considered to be statistically significant. All of the statistical analysis was conducted using the statistical package "netmeta" in R version 3.6.3 (R Core Team, Vienna, Austria).

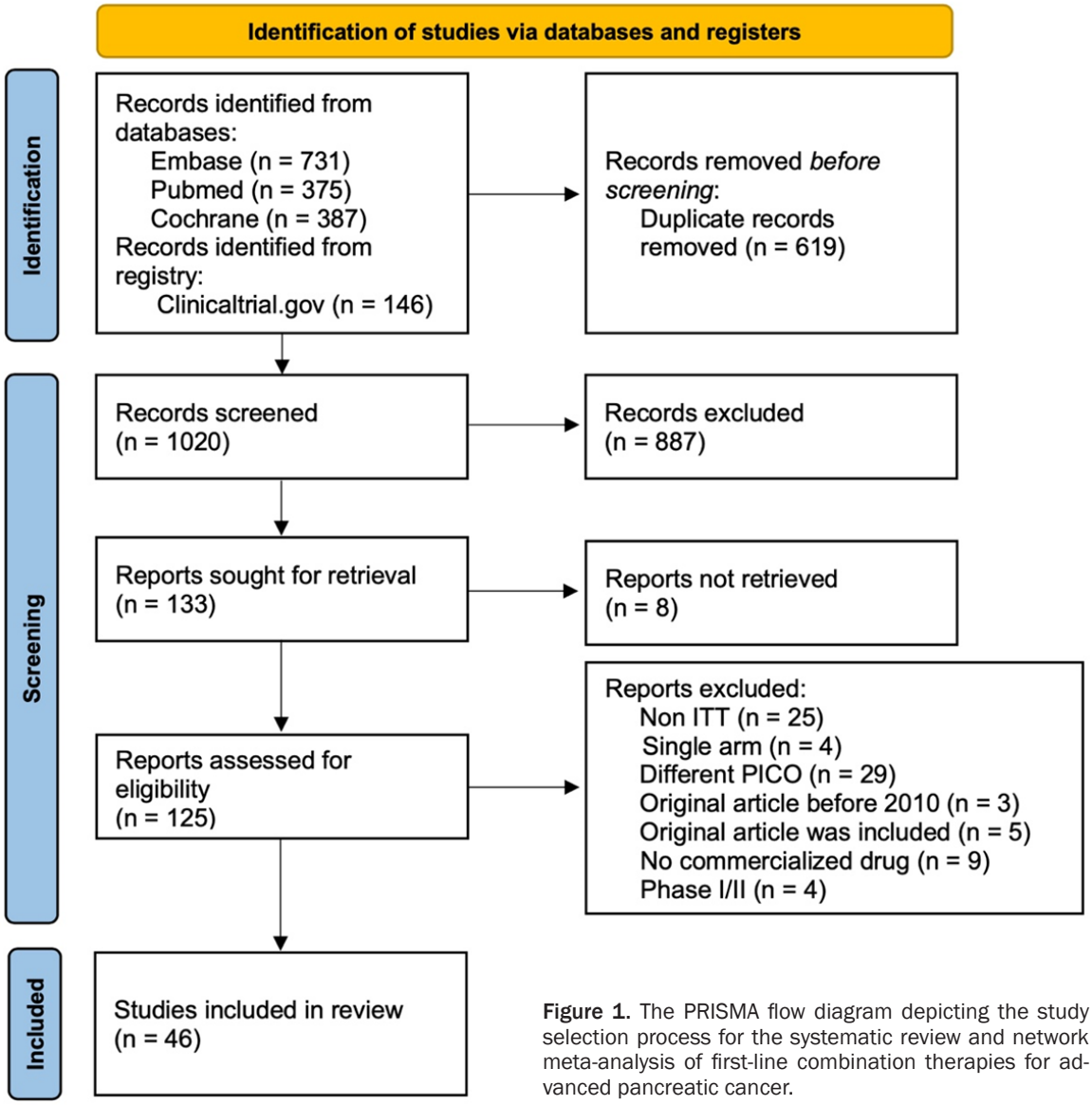

Figure 1. The PRISMA flow diagram depicting the study selection process for the systematic review and network meta-analysis of first-line combination therapies for advanced pancreatic cancer.

Results

Study selection and study characteristics

A total of 1020 articles were identified for article screening. These articles were initially screened by reviewing titles or abstracts and then furtherly retrieved for full articles. After retrieving full articles, 125 articles were assessed for eligibility. Finally, a total of 46 articles and 10,499 patients were enrolled into our SR-NMA (**Figure 1**). The RCTs included 12 phase 3 trials, 32 randomized phase 2 trials, and 2 phase 2/3 trials. Categorization details consisted of three main types of chemotherapy backbone, including 34 gemcitabine monotherapy, 8 with combined gemcitabine with nab-paclitaxel, 2 with 5-FU-based, and 1 with TKI-based. The baseline characteristics of the articles regarding author, year, trial phase, treatment arm, patient number, location of tumor, performance status (ECOG or KPS), and extent of disease were summarized in Supplementary Table 2.

Risk of bias, publication bias, and inconsistency assessment

The overall risk of bias was low in 28 articles. Fifteen articles were rated as some concern, and 3 articles were rated as high risk. The complete risk of bias assessment was summarized

in Supplementary Figure 1. The funnel plot with Egger's test for categorized treatments did not reveal significant publication bias for the four outcomes (Supplementary Figures 2, 3, 4, 5). The SIDE approach test did not reveal significant discrepancy between direct and indirect evidence for all the results (Supplementary Table 3). The design-by-treatment test for categorized treatments revealed significant inconsistency in the results of DCR (p-value = 0.01) (Supplementary Table 4).

Primary outcomes: OS and PFS

In terms of PFS, the net diagram presented in **Figure 2A** indicates that gemcitabine monotherapy was the most frequently used control arm among these clinical trials. **Figure 2B** displays the forest plot, which combines the results of both NMA and cNMA. The treatments were categorized into three main chemotherapy backbones and arranged in descending order based on their effect sizes. GA, GA with platinum and 5-FU (GA+Plat+FU), GA+other, G+Plat+FU, G+FU, FOLFIRINOX, FOLFIRINOX+mAB consistently demonstrated superior PFS in both NMA and cNMA results, with no significant heterogeneity between trials (I^2 = 36.9% and 53.1% for NMA and cNMA, respectively).

Likewise, significant OS benefits were found in treatment regimens including GA, GA+Plat+FU, FOLFIRINOX, FOLFIRINOX+mAB, G+Plat+FU, and G+FU except for GA+other. Of note, the treatment combinations with the most significant OS benefit were triplet or quadruplet, including FOLFIRINOX, GA+Plat+FU, and G+Plat+FU. The I^2 for heterogeneity of NMA and cNMA were 17.7% and 19.5%, respectively. The net diagram and forest plot in terms of OS are presented in **Figure 2C** and **2D**.

Secondary outcomes: ORR and DCR

The net diagram and forest plot for ORR are presented in **Figure 3A** and **3B**. In the GA-based treatment group, the combination of chemotherapy, TKI, hydroxychloroquine, or other medications exhibited better tumor response compared with gemcitabine monotherapy, except for the combination of monoclonal antibody (GA+mAB). Likewise, FU-based polychemotherapy, including FOLFIRINOX, also showed significantly superior response than gemcitabine monotherapy. In the gemcitabine-based treatment group, only the G+FU regimen demonstrated consistently favorable response in both NMA and cNMA results. In terms of DCR, similar results were found in the GA-based treatment group (**Figure 3C** and **3D**). G+FU, G+Plat+FU, and G+Plat+TKI, were three gemcitabine-based treatments with superior DCR compared with gemcitabine monotherapy. Among FU-based regimens, only FOLFIRINOX showed better DCR compared with gemcitabine monotherapy.

SUCRA ranking

The SUCRA results of NMA and cNMA for categorized treatments are presented in Supplementary Table 5. In terms of PFS and OS, G+Plat+FU, GA+Plat+FU and FOLFIRINOX were the top three combination treatments, indicating that three or four polychemotherapy combinations were associated with superior survival benefit.

Discussion

Through a comprehensive overview of randomized trials with intent-to-treat analysis in first-line settings of advanced PDAC, this NMA evaluated the clinical efficacy of various combined treatments based on chemotherapy backbone including gemcitabine, gemcitabine/nab-paclitaxel, or 5-FU. In gemcitabine-based chemotherapy, the addition of 5-FU derivatives consistently demonstrated superior benefit across all clinical outcomes. However, adding platinum to gemcitabine-based chemotherapy did not significantly improve overall response rate, PFS, and OS. These findings suggest that 5-FU derivatives may be more suitable in combination with gemcitabine than platinum. As expected, the inclusion of both 5-FU derivatives and platinum in gemcitabine-based chemotherapy, including gemcitabine/nab-paclitaxel, also resulted in the significant improvement of tumor response and prognosis.

5-FU-based combination treatment with both oxaliplatin and irinotecan (FOLFIRINOX) has been established as one of the first-line chemotherapy regimens for metastatic PDAC [6]. Consistent with these results, 5-FU as the backbone of polychemotherapy such as FOLFIRI with gemcitabine or FOLFIRINOX demonstrated superior efficacy compared to gemcitabine monotherapy in our study. Of note,

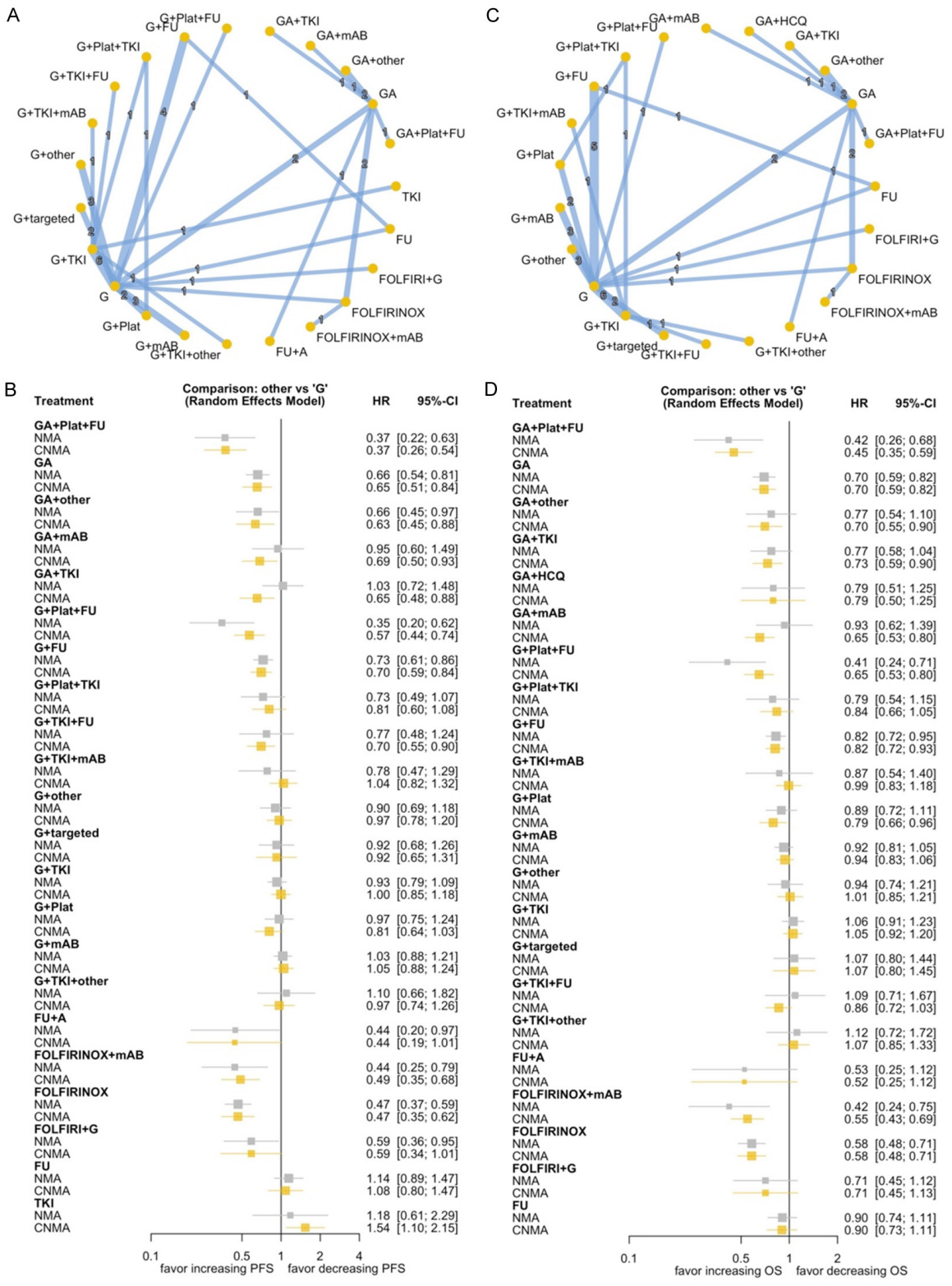

Figure 2. A. The network meta-analysis (NMA) net diagram of overall survival (OS) for categorized first-line combination treatments in advanced pancreatic cancer. B. The NMA and component NMA (cNMA) forest plot of OS for categorized first-line combination treatments in advanced pancreatic cancer. The hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for each treatment comparison, with the reference treatment being gemcitabine monotherapy. C. The NMA net diagram of progression-free survival (PFS) for categorized first-line combination treatments in advanced pancreatic cancer. D. The NMA and cNMA forest plot of PFS for categorized first-line

combination treatments in advanced pancreatic cancer. The HRs and 95% CIs are presented for each treatment comparison, with the reference treatment being gemcitabine monotherapy. G indicates gemcitabine; GA, gemcitabine + nab-paclitaxel; Plt, platinum; FU, fluorouracil; mAB, monoclonal antibodies; TKI, tyrosine kinase inhibitor; HCQ, hydroxychloroquine; FOLFIRINOX, folinic acid + fluorouracil + irinotecan + oxaliplatin; FOLFIRI, folinic acid + fluorouracil + irinotecan.

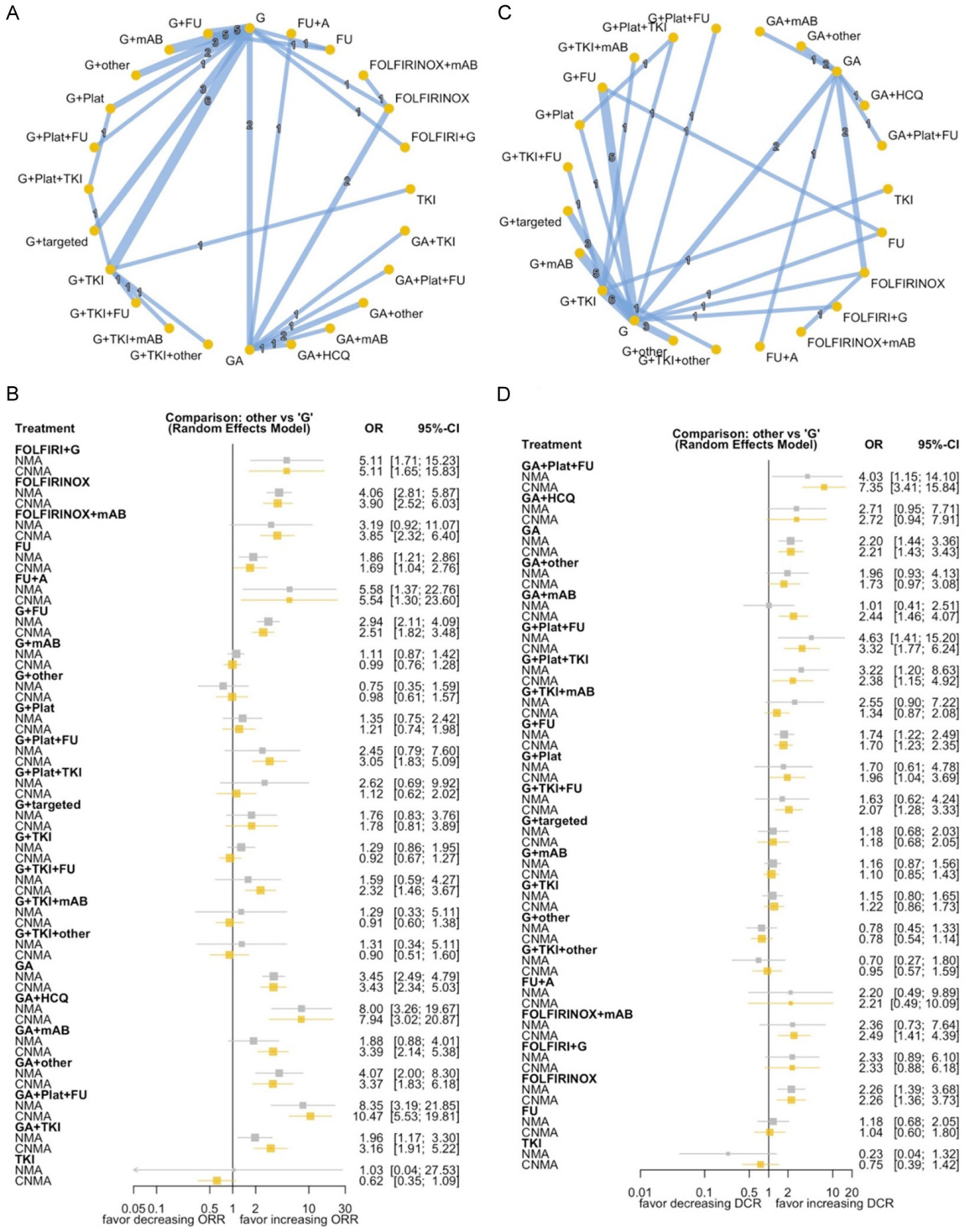

Figure 3. A. The NMA net diagram of overall response rate (ORR) for categorized first-line combination treatments in advanced pancreatic cancer. B. The NMA and cNMA forest plot of ORR for categorized first-line combination

treatments in advanced pancreatic cancer. The odds ratios (ORs) and 95% CIs are presented for each treatment comparison, with the reference treatment being gemcitabine monotherapy. C. The NMA net diagram of disease control rate (DCR) for categorized first-line combination treatments in advanced pancreatic cancer. D. The NMA and cNMA forest plot of DCR for categorized first-line combination treatments in advanced pancreatic cancer. The ORs and 95% CIs are presented for each treatment comparison, with the reference treatment being gemcitabine monotherapy. G indicates gemcitabine; GA, gemcitabine + nab-paclitaxel; Plt, platinum; FU, fluorouracil; mAB, monoclonal antibodies; TKI, tyrosine kinase inhibitor; HCQ, hydroxychloroquine; FOLFIRINOX, folinic acid + fluorouracil + irinotecan + oxaliplatin; FOLFIRI, folinic acid + fluorouracil + irinotecan.

5-FU in combination with nab-paclitaxel also showed promising response rate and better survival compared with gemcitabine alone. Taken together, our results demonstrated the potential role of 5-FU adding to gemcitabine and/or nab-paclitaxel.

Early trials have investigated the triplet combination of S-1, gemcitabine, and nab-paclitaxel (GAS) for the treatment of advanced PDAC [18-21]. The dose-limiting toxicities in these phase I trials included grade 3 or 4 neutropenia, grade 3 thrombocytopenia, grade 3 rash, and grade 3 mucositis. In a single-arm phase 2 trial, the overall response rate was 43% with median OS of 41 months for borderline resectable PDAC [19]. The most common adverse events were hematologic toxicities, including 25% grade ≥3 neutropenia. These trials demonstrated manageable toxicities of GAS regimen with encouraging preliminary tumor response, which warrants further trials to evaluate the clinical efficacy.

Several targeted drugs have been investigated in combination with gemcitabine-based chemotherapy in PDAC. Erlotinib, a small molecule tyrosine kinase inhibitor targeting epidermal growth factor receptor, in combination with gemcitabine has shown a significant but small survival increment compared with gemcitabine alone (median 6.24 months versus 5.91 months) [22]. Other targeted drugs such as small molecule inhibitors and monoclonal antibodies have also been investigated in randomized phase II trials. Although some drugs combined with gemcitabine have shown inspiring tumor response with acceptable toxicities, there have been no phase III trials to confirm their clinical benefit. Correspondingly, our study also showed that targeted drugs or non-chemotherapy drugs along with gemcitabine did not significantly improve the disease control.

The strength of NMA is to investigate the optimal intervention among different comparisons. In our study, most of enrolled regiments contained chemotherapy, targeted therapy, or other therapy, the complicated drug-drug interactions among these drugs have not been well established. To investigate this issue, we applied the cNMA to estimate the effect of each component and its potential combined effect. This statistical approach is relatively rare being applied and was firstly introduced in the field of psychology [23]. Through this analysis, we can provide medical oncologists and physicians the clinically effective chemotherapy regiments. By knowing the most effective component, it may provide trial designers certain ideas for future direction of clinical trials, either in the setting of curative-intended or palliative.

This study has some limitations. First, the heterogeneity of studies included in the analysis may have influenced the results despite efforts to account for these confounding factors in the statistical methods. Nevertheless, it is worth noting that the I^2 statistics, which assess heterogeneity, did not indicate substantial variability in the outcomes in NMA analysis ($I^2 \leq 50\%$). Second, due to the lack of safety data, we were unable to perform a benefit-harm assessment, which precluded an evaluation of quality of life. Third, the combination of targeted drugs based on their drug modality, rather than their distinct mechanisms of action, may have introduced some degree of bias in the analysis of their combined effects. Fourth, racial differences were not explicitly considered in the analysis, which may limit the generalizability of these findings. Under this circumstance, the GRADE assessment for certainty of evidence is also not available.

Conclusion

Gemcitabine-based or 5-FU-based combination chemotherapy were two significantly effective treatments for advanced PDAC. Notably, gemcitabine-based treatment in combination

with 5-FU showed superior efficacy than with platinum. Among polychemotherapy regimens, triplet or quadruplet were associated with more favorable survival benefit. These results suggested that a triplet regimen combining gemcitabine, nab-paclitaxel, and 5-FU may be a promising treatment option for advanced PDAC and warrants further exploration.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Details of text search

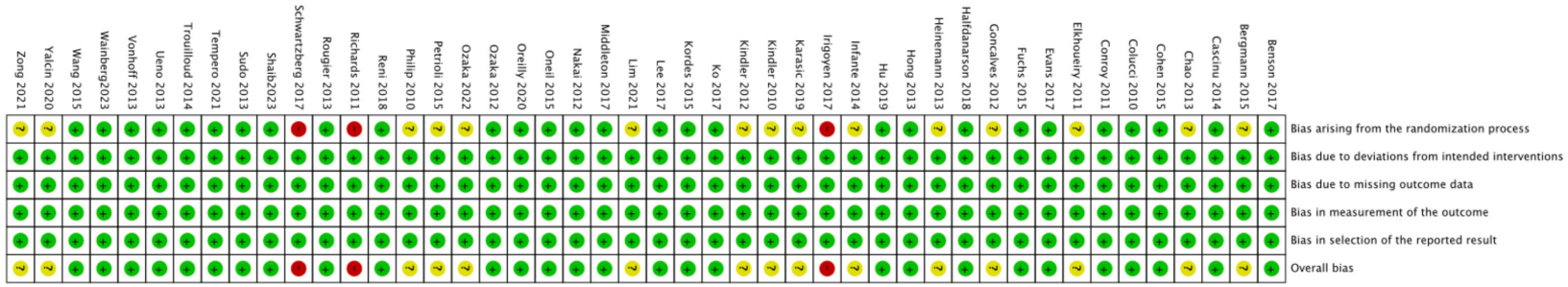
Pubmed	
“pancreatic neoplasms”[MeSH Terms] AND (“advance”[All Fields] OR “advanced”[All Fields] OR “advancement”[All Fields] OR “advancements”[All Fields] OR “advances”[All Fields] OR “advancing”[All Fields] OR ((“focal”[All Fields] OR “focalities”[All Fields] OR “focality”[All Fields] OR “focalization”[All Fields] OR “focalized”[All Fields] OR “focally”[All Fields] OR “focals”[All Fields] OR “local”[All Fields] OR “localisation”[All Fields] OR “localisations”[All Fields] OR “localise”[All Fields] OR “localised”[All Fields] OR “localises”[All Fields] OR “localising”[All Fields] OR “localization”[All Fields] OR “localizations”[All Fields] OR “localize”[All Fields] OR “localized”[All Fields] OR “localizer”[All Fields] OR “localizers”[All Fields] OR “localizes”[All Fields] OR “localizing”[All Fields] OR “locally”[All Fields] OR “locals”[All Fields]) AND (“advance”[All Fields] OR “advanced”[All Fields] OR “advancement”[All Fields] OR “advancements”[All Fields] OR “advances”[All Fields] OR “advancing”[All Fields])) OR (“unresectability”[All Fields] OR “unresectable”[All Fields] OR “unresected”[All Fields]) OR (“metastatically”[All Fields] OR “metastatics”[All Fields] OR “metastatization”[All Fields] OR “metastatize”[All Fields] OR “metastatized”[All Fields] OR “metastatizing”[All Fields] OR “secondary”[MeSH Subheading] OR “secondary”[All Fields] OR “metastatic”[All Fields])) AND (“chemotherapy s”[All Fields] OR “drug therapy”[MeSH Terms] OR (“drug”[All Fields] AND “therapy”[All Fields]) OR “drug therapy”[All Fields] OR “chemotherapies”[All Fields] OR “drug therapy”[MeSH Subheading] OR “chemotherapy”[All Fields]) AND “randomized controlled trial”[Publication Type]	
Cochrane library	
(“pancreatic neoplasms”[MeSH Terms] AND (“advance”[All Fields] OR “advanced”[All Fields] OR “advancement”[All Fields] OR “advancements”[All Fields] OR “advances”[All Fields] OR “advancing”[All Fields] OR ((“focal”[All Fields] OR “focalities”[All Fields] OR “focality”[All Fields] OR “focalization”[All Fields] OR “focalized”[All Fields] OR “focally”[All Fields] OR “focals”[All Fields] OR “local”[All Fields] OR “localisation”[All Fields] OR “localisations”[All Fields] OR “localise”[All Fields] OR “localised”[All Fields] OR “localises”[All Fields] OR “localising”[All Fields] OR “localization”[All Fields] OR “localizations”[All Fields] OR “localize”[All Fields] OR “localized”[All Fields] OR “localizer”[All Fields] OR “localizers”[All Fields] OR “localizes”[All Fields] OR “localizing”[All Fields] OR “locally”[All Fields] OR “locals”[All Fields]) AND (“advance”[All Fields] OR “advanced”[All Fields] OR “advancement”[All Fields] OR “advancements”[All Fields] OR “advances”[All Fields] OR “advancing”[All Fields])) OR (“unresectability”[All Fields] OR “unresectable”[All Fields] OR “unresected”[All Fields]) OR (“metastatically”[All Fields] OR “metastatics”[All Fields] OR “metastatization”[All Fields] OR “metastatize”[All Fields] OR “metastatized”[All Fields] OR “metastatizing”[All Fields] OR “secondary”[MeSH Subheading] OR “secondary”[All Fields] OR “metastatic”[All Fields])) AND (“chemotherapy s”[All Fields] OR “drug therapy”[MeSH Terms] OR (“drug”[All Fields] AND “therapy”[All Fields]) OR “drug therapy”[All Fields] OR “chemotherapies”[All Fields] OR “drug therapy”[MeSH Subheading] OR “chemotherapy”[All Fields]) AND “randomized controlled trial”[Publication Type]) AND ((randomizedcontrolledtrial[Filter]) AND (2010:2024[pdat]))	
Embase	
1	(‘pancreas tumor’/exp OR ‘pancreas neoplasia’ OR ‘pancreas neoplasm’ OR ‘pancreas tumor’ OR ‘pancreas tumour’ OR ‘pancreatic neoplasm’ OR ‘pancreatic neoplasms’ OR ‘pancreatic tumor’ OR ‘pancreatic tumour’ OR ‘locally advanced pancreatic cancer’/exp OR ‘advanced pancreatic cancer’/exp OR ‘unresectable pancreatic cancer’/exp OR ‘metastatic pancreatic cancer’/exp) AND ‘chemotherapy’/exp AND (‘randomized controlled trial’/exp OR ‘controlled trial, randomized’ OR ‘randomised controlled study’ OR ‘randomised controlled trial’ OR ‘randomized controlled study’ OR ‘randomized controlled trial’ OR ‘trial, randomized controlled’)
#2	#1 AND ‘Article’/it
#3	#1 AND ‘Article’/it AND (‘clinical trial’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘phase 2 clinical trial’/de OR ‘phase 2 clinical trial topic’/de OR ‘phase 3 clinical trial’/de OR ‘phase 3 clinical trial topic’/de OR ‘prospective study’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial topic’/de)
#4	#1 AND ‘article’/it AND (‘clinical trial’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘phase 2 clinical trial’/de OR ‘phase 2 clinical trial topic’/de OR ‘phase 3 clinical trial’/de OR ‘phase 3 clinical trial topic’/de OR ‘prospective study’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial topic’/de) AND [2010-2024]/py

Supplementary Table 2. The baseline characteristics of enrolled articles

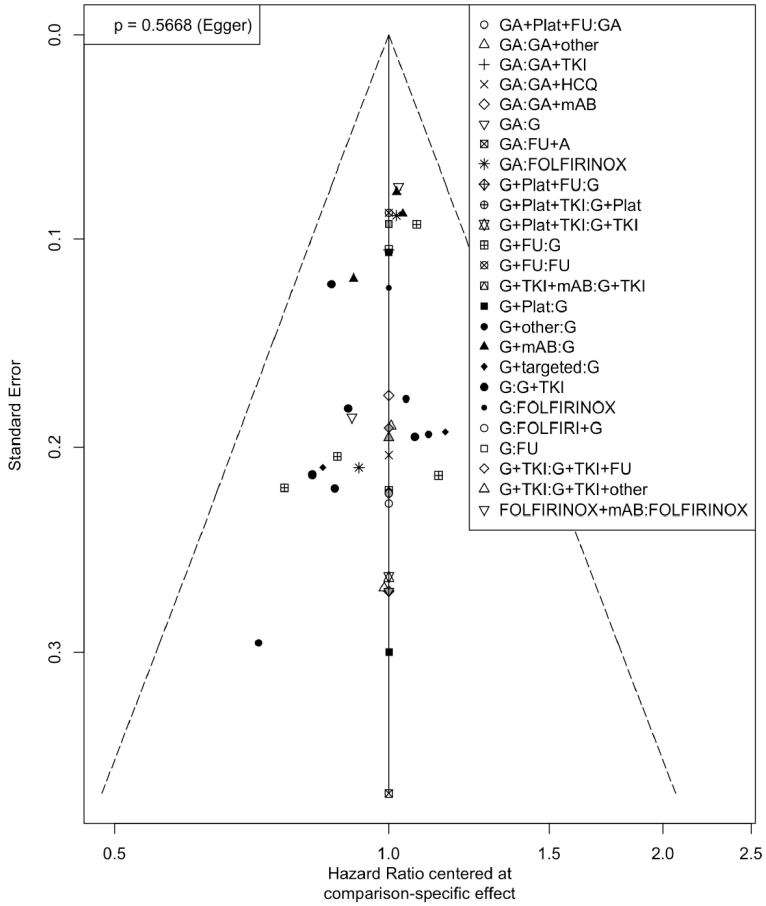
Author	Year	Phase	Treatment arm	n	Tumor location	ECOG/KPS	Extent of disease	PMID
Colucci	2010	III	Gemcitabine+Cisplatin vs Gemcitabine	201 vs 199	Head, body, tail	≥50	Unresectable locally advanced or metastatic	20194854
Kindler	2010	III	Gemcitabine+Bevacizumab vs Gemcitabine	302 vs 300	No information	0-2	Unresectable locally advanced or metastatic	20606091
Philip	2010	III	Gemcitabine+Cetuximab vs Gemcitabine	372 vs 371	No information	0-2	Unresectable locally advanced or metastatic	20606093
Conroy	2011	II/III	FOLFIRINOX vs Gemcitabine	171 vs 171	Head, body, tail, diffuse	0-2	Metastatic	21561347
Richards	2011	II	Gemcitabine+Enzastaurin vs Gemcitabine	86 vs 44	No information	0-2	Unresectable locally advanced or metastatic	19714296
El-Khoueiry	2011	II	Gemcitabine+Sorafenib vs Sorafenib	37 vs 15	No information	0-1	Metastatic	21424698
Gonçalves	2012	III	Gemcitabine+Sorafenib vs Gemcitabine	52 vs 52	No information	0-2	Unresectable locally advanced or metastatic	22771827
Kindler	2012	II	Gemcitabine+Ganitumab vs Gemcitabine+Conatumumab vs Gemcitabine	42 vs 41 vs 42	Head, neck, tail, other	0-1	Metastatic	22700995
Nakai	2012	II	Gemcitabine+S-1 vs Gemcitabine	53 vs 53	Head, body, tail	0-2	Unresectable locally advanced or metastatic	22555398
Ozaka	2012	II	Gemcitabine+S-1 vs Gemcitabine	57 vs 59	No information	0-2	Unresectable locally advanced or metastatic	22249272
Chao	2013	II	Gemcitabine+Cisplatin vs Gemcitabine	21 vs 25	Head, body, tail	≥50	Metastatic	23912692
Heinemann	2013	II	Gemcitabine+Upamostat (400 mg) vs Gemcitabine+Upamostat (200 mg) vs Gemcitabine	31 vs 31 vs 33	Head, body, tail	0-1	Unresectable locally advanced	23412098
Rougier	2013	III	Gemcitabine+Aflibercept vs Gemcitabine	271 vs 275	Head, body, tail, diffuse	0-2	Metastatic	23642329
Ueno	2013	III	Gemcitabine+S-1 vs S-1 vs Gemcitabine	275 vs 280 vs 277	Head, body, tail	0-1	Unresectable locally advanced or metastatic	23547081
Von Hoff	2013	III	Gemcitabine+nab-Paclitaxel vs Gemcitabine	431 vs 430	Head, body, tail, other	≥70	Metastatic	24131140
Hong	2013	II	Gemcitabine+Simvastatin vs Gemcitabine	58 vs 56	No information	0-2	Unresectable locally advanced or metastatic	24162380
Sudo	2013	III	Gemcitabine+S-1 vs Gemcitabine	51 vs 50	Head, body, tail	0-1	Unresectable locally advanced or metastatic	24322377
Cascinu	2014	II	Gemcitabine+Cisplatin+Sorafenib vs Gemcitabine+Cisplatin	58 vs 56	Head, other	≥70	Unresectable locally advanced or metastatic	24189171
Infante	2014	II	Gemcitabine+Trametinib vs Gemcitabine	80 vs 80	No information	0-1	Metastatic	24915778
Trouilloud	2014	II	FOLFIRI+Gemcitabine vs Gemcitabine	49 vs 49	Head, body, tail	0-1	Metastatic	25454414
Bergmann	2015	II	Gemcitabine+Sunitinib vs Gemcitabine	52 vs 54	Head, body, tail, other	0-1	Unresectable locally advanced or metastatic	25459392
Fuchs	2015	III	Gemcitabine+Ganitumab (20 mg) vs Gemcitabine+Ganitumab (12 mg) vs Gemcitabine	160 vs 318 vs 322	Head, body, tail	0-1	Metastatic	25609246
Kordes	2015	II	Gemcitabine+Erlotinib+Metformin vs Gemcitabine+Erlotinib	60 vs 61	Head, body	0-2	Unresectable locally advanced or metastatic	26067687
O'Neil	2015	II/III	Gemcitabine+Rigosertib vs Gemcitabine	106 vs 54	No information	0-2	Metastatic	26091808
Petrioli	2015	II	Gemcitabine+Capecitabine+Oxaliplatin vs Gemcitabine	34 vs 33	No information	0-2	Metastatic	25618415
Wang	2015	II	Gemcitabine+Erlotinib vs Gemcitabine	44 vs 44	No information	0-2	Metastatic	26046796
Cohen	2015	II	Gemcitabine+Imexon vs Gemcitabine	72 vs 70	No information	0-1	Metastatic	26709865
Benson	2017	II	Gemcitabine+Simtuzumab (700 mg) vs Gemcitabine+Simtuzumab (200 mg) vs Gemcitabine	79 vs 76 vs 81	No information	0-1	Metastatic	28246206
Evans	2017	II	Gemcitabine+Dasatinib vs Gemcitabine	100 vs 102	Head, body, tail	0-1	Unresectable locally advanced	27998964
Irigoyen	2017	II	Gemcitabine+Erlotinib+Capecitabine vs Gemcitabine+Erlotinib	60 vs 60	No information	0-2	Metastatic	28222309
Ko	2017	II	Gemcitabine+nab-Paclitaxel+Apatorsen vs Gemcitabine+nab-Paclitaxel	66 vs 66	No information	0-1	Metastatic	28935773
Lee	2017	III	Gemcitabine+Capecitabine vs Gemcitabine	108 vs 106	Head, body, tail, diffuse	0-2	Unresectable locally advanced or metastatic	28072706

Middleton	2017	II	Gemcitabine+Vandetanib vs Gemcitabine	72 vs 70	Head, uncinate, body, tail	0-2	Unresectable locally advanced or metastatic	28259610
Schwartzberg	2017	II	Gemcitabine+Kanglaite vs Gemcitabine	45 vs 22	No information	0-2	Unresectable locally advanced or metastatic	28819385
Reni	2018	II	Gemcitabine+nab-Paclitaxel+Cisplatin+Capecitabine vs Gemcitabine+nab-Paclitaxel	42 vs 41	Head, body, tail	≥70	Metastatic	30220407
Halfdanarson	2018	II	Gemcitabine+Erlotinib+Panitumumab vs Gemcitabine+Erlotinib	46 vs 46	No information	0-1	Metastatic	30679315
Hu	2019	II	Gemcitabine+nab-Paclitaxel+Tarextumab vs Gemcitabine+nab-Paclitaxel	89 vs 88	Head, body, tail, other	0-1	Metastatic	31347292
Karasic	2019	II	Gemcitabine+nab-Paclitaxel+ Hydroxychloroquine vs Gemcitabine+nab-Paclitaxel	55 vs 57	Head, body, tail	0-1	Metastatic	31120501
O'Reilly	2020	II	Gemcitabine+nab-Paclitaxel+Necuparanib vs Gemcitabine+nab-Paclitaxel	62 vs 58	No information	0-1	Metastatic	32361265
Yalcin	2020	II	Gemcitabine+nab-Paclitaxel vs Gemcitabine	62 vs 63	Head, body, tail	0-1	Unresectable locally advanced or metastatic	32228512
Lim	2021	II	Gemcitabine+Erlotinib+Oxaliplatin vs Gemcitabine+Erlotinib	33 vs 32	Head, uncinate, body, tail	0-2	Unresectable locally advanced or metastatic	34296544
Tempero	2021	III	Gemcitabine+nab-Paclitaxel+Ibrutinib vs Gemcitabine+nab-Paclitaxel	211 vs 213	No information	0-1	Metastatic	33539945
Zong	2021	II	S-1+nab-Paclitaxel vs Gemcitabine+nab-Paclitaxel	20 vs 20	Head, body, tail	0-1	Unresectable locally advanced or metastatic	33191450
Ozaka	2022	II	Gemcitabine+nab-Paclitaxel vs FOLFIRINOX	63 vs 62	Head, body, tail	0-1	Unresectable locally advanced	36652891
Shaib	2023	II	FOLFIRINOX+Ramucirumab vs FOLFIRINOX	42 vs 40	No information	0-1	Metastatic	37268519
Wainberg	2023	III	NALIRIFOX vs Gemcitabine+nab-Paclitaxel	383 vs 387	Head, other	0-1	Metastatic	37708904

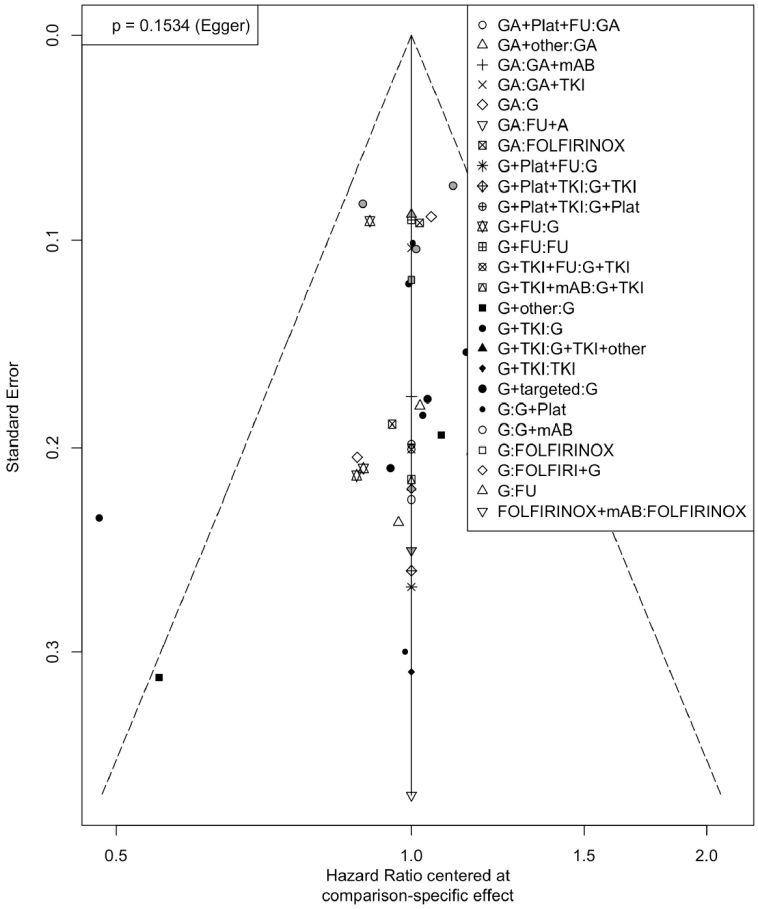
FOLFIRINOX, Folinic acid, fluorouracil, irinotecan, oxaliplatin; FOLFIRI, Folinic acid, fluorouracil, irinotecan.



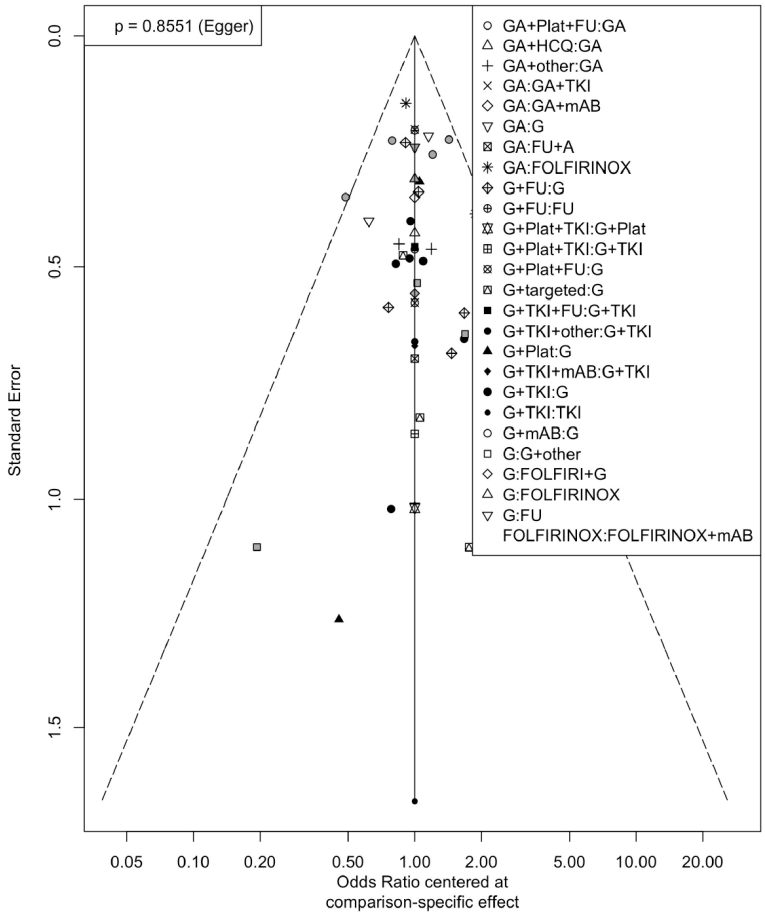
Supplementary Figure 1. Risk of bias summary for the included randomized controlled trials, assessed using the Cochrane Risk of Bias Tool. The risk of bias is evaluated across six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.



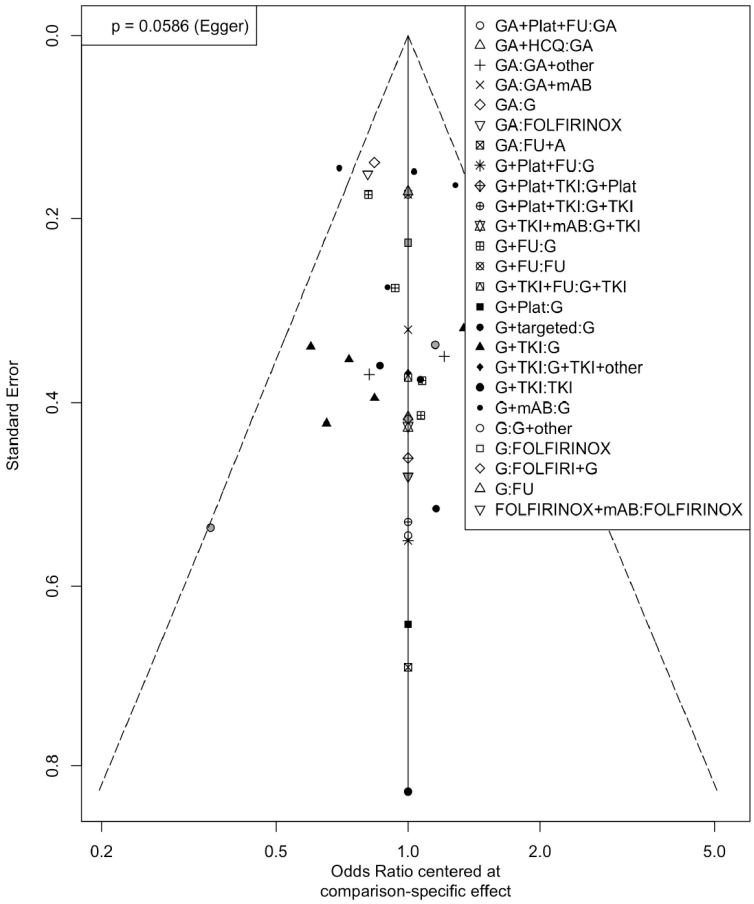
Supplementary Figure 2. The NMA funnel plot assessing publication bias for OS among categorized first-line combination treatments in advanced pancreatic cancer.



Supplementary Figure 3. The NMA funnel plot assessing publication bias for PFS among categorized first-line combination treatments in advanced pancreatic cancer.



Supplementary Figure 4. The NMA funnel plot assessing publication bias for ORR among categorized first-line combination treatments in advanced pancreatic cancer.



Supplementary Figure 5. The NMA funnel plot assessing publication bias for DCR among categorized first-line combination treatments in advanced pancreatic cancer.

Supplementary Table 4. The design-by-treatment test for consistency for categorized treatments

	Q of within designs	*p*-value	Q of between designs	*p*-value	Q of total	*p*-value
OS	22.85	0.15	1.13	0.77	23.98	0.24
PFS	24.46	0.07	5.59	0.13	30.05	0.05
ORR	19.69	0.48	1.39	0.71	21.08	0.58
DCR	38.07	0.005	1.86	0.60	39.93	0.01

Supplementary Table 5. The SUCRA of OS, PFS, ORR, DCR for categorized treatments

SUCRA of OS				SUCRA of PFS			
	NMA		cNMA		NMA		cNMA
GA+Plat+FU	0.9273	GA+Plat+FU	0.9756	G+Plat+FU	0.9341	GA+Plat+FU	0.9701
G+Plat+FU	0.9252	FOLFIRINOX+mAB	0.9049	GA+Plat+FU	0.9251	FOLFIRINOX	0.9000
FOLFIRINOX+mAB	0.9163	FOLFIRINOX	0.8521	FOLFIRINOX+mAB	0.8603	FOLFIRINOX+mAB	0.8657
FOLFIRINOX	0.8239	FU+A	0.8140	FOLFIRINOX	0.8596	FU+A	0.8431
FU+A	0.7943	G+Plat+FU	0.7628	FU+A	0.8314	G+Plat+FU	0.7763
GA	0.6997	GA+mAB	0.7545	FOLFIRI+G	0.7201	FOLFIRI+G	0.7124
FOLFIRI+G	0.6319	GA	0.6781	GA	0.6708	GA+other	0.6811
GA+TKI	0.5688	GA+other	0.6562	GA+other	0.6533	GA+TKI	0.6535
GA+other	0.5626	FOLFIRI+G	0.6227	G+FU	0.5948	GA	0.6510
G+Plat+TKI	0.5423	GA+TKI	0.6078	G+Plat+TKI	0.5814	GA+mAB	0.5931
GA+HCQ	0.5192	G+Plat	0.5183	G+TKI+FU	0.5165	G+TKI+FU	0.5875
G+FU	0.5128	GA+HCQ	0.4948	G+TKI+mAB	0.5036	G+FU	0.5827
G+TKI+mAB	0.4288	G+FU	0.4860	G+other	0.3696	G+Plat+TKI	0.4496
G+Plat	0.3934	G+Plat+TKI	0.4397	G+targeted	0.3440	G+Plat	0.4464
FU	0.3732	G+TKI+FU	0.4070	G+TKI	0.3410	G+targeted	0.3133
G+mAB	0.3445	FU	0.3393	GA+mAB	0.3222	G+TKI+other	0.2625
GA+mAB	0.3364	G+mAB	0.2833	G+Plat	0.2907	G+other	0.2595
G+other	0.3144	G+TKI+mAB	0.2001	G	0.2428	G+TKI	0.2221
G	0.2138	G+other	0.1798	GA+TKI	0.2278	G	0.2192
G+TKI+FU	0.1857	G	0.1783	G+mAB	0.2092	G+TKI+mAB	0.1732
G+targeted	0.1673	G+targeted	0.1328	G+TKI+other	0.2005	G+mAB	0.1699
G+TKI+other	0.1658	G+TKI+other	0.1074	TKI	0.1805	FU	0.1634
G+TKI	0.1521	G+TKI	0.1044	FU	0.1206	TKI	0.0043
SUCRA of ORR				SUCRA of DCR			
	NMA		cNMA		NMA		cNMA
GA+Plat+FU	0.9272	GA+Plat+FU	0.9721	G+Plat+FU	0.8811	GA+Plat+FU	0.9927
GA+HCQ	0.9234	GA+HCQ	0.9267	GA+Plat+FU	0.8457	G+Plat+FU	0.8605
FU+A	0.8088	FU+A	0.8128	G+Plat+TKI	0.8021	FOLFIRINOX+mAB	0.7424
FOLFIRI+G	0.8050	FOLFIRI+G	0.8112	GA+HCQ	0.7304	GA+mAB	0.7366
FOLFIRINOX	0.7768	FOLFIRINOX	0.7768	G+TKI+mAB	0.7067	GA+HCQ	0.7321
GA+other	0.7574	FOLFIRINOX+mAB	0.7653	FOLFIRINOX	0.6842	G+Plat+TKI	0.7010
GA	0.6972	GA	0.7026	GA	0.6723	FOLFIRINOX	0.6737
FOLFIRINOX+mAB	0.6393	GA+mAB	0.6898	FOLFIRI+G	0.6715	GA	0.6684
G+FU	0.6331	GA+other	0.6881	FOLFIRINOX+mAB	0.6645	FOLFIRI+G	0.6665
G+Plat+TKI	0.5650	GA+TKI	0.6534	FU+A	0.6176	G+TKI+FU	0.6408
G+Plat+FU	0.5421	G+Plat+FU	0.6532	GA+other	0.5973	FU+A	0.6084
GA+TKI	0.4474	G+FU	0.5536	G+FU	0.5507	G+Plat	0.5766
GA+mAB	0.4254	G+TKI+FU	0.5166	G+Plat	0.5190	G+FU	0.5055
FU	0.4254	G+targeted	0.4305	G+TKI+FU	0.5028	GA+other	0.5035
G+targeted	0.4024	FU	0.4075	G+targeted	0.3258	G+TKI+mAB	0.3731
G+TKI+FU	0.3620	G+Plat	0.2977	FU	0.3256	G+TKI	0.3030
TKI	0.3306	G+Plat+TKI	0.2558	G+mAB	0.3163	G+targeted	0.2877
G+TKI+other	0.3015	G	0.2040	G+TKI	0.3074	G+mAB	0.2370
G+TKI+mAB	0.2961	G+mAB	0.1976	GA+mAB	0.2647	FU	0.2226
G+Plat	0.2795	G+other	0.1974	G	0.2132	G	0.1712
G+TKI	0.2571	G+TKI	0.1569	G+TKI+other	0.1377	G+TKI+other	0.1640
G+mAB	0.1860	G+TKI+other	0.1540	G+other	0.1330	TKI	0.0699
G	0.1278	G+TKI+mAB	0.1512	TKI	0.0305	G+other	0.0630
G+other	0.0836	TKI	0.0252				